Effect of Incretin Analogues and Dipeptidyl-peptidase-IV inhibitors on the risk of thyroid cancer

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Study | Finalised

Administrative details

PURI
https://redirect.ema.europa.eu/resource/107225

EU PAS number
EUPAS107225

Study ID
107225

DARWIN EU® study
No

Study countries
United States

Study description
Incretin based therapies are commonly used as second-line antihyperglycemic drugs in the treatment of type 2 diabetes mellitus. They promote glucose dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and promote satiety or potentiate the action of incretin hormones by blocking DPP-IV – the enzyme responsible for the degradation of incretin hormones. Activation of the GLP-1 receptor has been shown to cause thyroid C-cell hyperplasia and C-cell tumors in carcinogenicity studies in preclinical studies using rodents prompting the U.S. Food and Drug Administration (FDA) to issue a warning regarding medullary thyroid cancer for long-acting GLP-1RA. Still, the relevance of

these findings in humans is questionable, as there is a discrepancy in the level of expression and biology of GLP-1 receptors in the thyroid between rodents and primates. Currently, there remains uncertainty about the risk of thyroid cancer associated with the use of incretin (GLP-1)-based therapies with data from clinical and observational studies showing conflicting results. Some studies have reported no increased risk of thyroid cancer with the use of GLP-1RA relative to placebo or other antihyperglycemic drugs, while a recent study found an increased risk of all thyroid cancer and medullary thyroid cancer, particularly after 1-3 years of treatment. Most of the existing studies suffer from methodological issues, including short durations of follow-up, limited lag period, uncertainty about valid ascertainment of outcomes, diagnostic suspicion, insufficient confounding control, incomplete covariate ascertainment and inadequate power. Additionally, most studies so far have only focused on the effect of exenatide and liraglutide on thyroid cancer. This work, therefore, aims to address these issues, and contribute critical evidence to inform clinical decision-making by exploring the effect of GLP-1RA and DPP-IV inhibitors on thyroid cancer incidence.

Study status
Finalised

Research institution and networks

Institutions

University of North Carolina at Chapel Hill
First published: 01/02/2024
Last updated 01/02/2024
Institution

Contact details

Study institution contact
Til Stürmer
Study contact

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Primary lead investigator
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Study timelines

Date when funding contract was signed
Planned:
29/06/2022
Actual:
29/06/2022

Study start date
Planned:
29/06/2022
Actual:
29/06/2022

Date of final study report
Planned:
31/12/2024
Actual:
17/10/2023

Sources of funding

- Other

More details on funding

National Institute on Aging at NIH

Study protocol

Effect of Incretin Analogs on risk of thyroid cancer.pdf(276.24 KB)

Regulatory

Was the study required by a regulatory body?
No

Is the study required by a Risk Management Plan (RMP)?
Not applicable

Methodological aspects

Study type

Study type list

Study topic:
Disease /health condition
Human medicinal product

Study type:
Non-interventional study

Scope of the study:
Drug utilisation

Data collection methods:
Secondary data collection

Main study objective:
To estimate the comparative effect of GLP-1RA and DPP-IV inhibitors versus sodium-glucose cotransporter-2 (SGLT-2) inhibitors on the incidence of thyroid cancer.

Study Design

Non-interventional study design
Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code
(A10AE) Insulins and analogues for injection, long-acting
(A10BH) Dipeptidyl peptidase 4 (DPP-4) inhibitors
(A10BJ) Glucagon-like peptide-1 (GLP-1) analogues
(A10BK) Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Medical condition to be studied
Type 2 diabetes mellitus

Population studied

Short description of the study population
The study population involved patients aged 66 years or older, prescribed with GLP-1RA, DPP-IV inhibitors or SGLT-2 inhibitors between January 1, 2008, and December 31, 2018 identified from the Medicare Fee-for-Service Database.

Age groups
Adults (65 to < 75 years)
Adults (75 to < 85 years)
Adults (85 years and over)

Special population of interest
Frail population

Estimated number of subjects
100000

Study design details

Outcomes
The primary outcome is thyroid cancer (TC).

Data analysis plan
The main effect measure estimate will be standardized incidence rate differences (IRD) with the assumption that there is no unmeasured confounding. We will also estimate IRD within different times after antihyperglycemic drug initiation to allow for incidence rates to vary over time. Secondary effect measure will be hazard ratios. When estimating risks of cancer outcomes in older Medicare patients, censoring those who died prior to having the outcome of interest, as commonly done in survival analyses, could introduce bias in the risk estimation. To avoid this, we will employ Aalen Johansen (AJ) estimators to estimate risks.

Data management

Data sources

Data source(s), other
Medicare Fee-for-Service (FFS) Database

Data sources (types)
Administrative data (e.g. claims)

Use of a Common Data Model (CDM)

CDM mapping
No

Data quality specifications

Check conformance
Unknown

Check completeness
Unknown

Check stability
Unknown

Check logical consistency
Unknown

Data characterisation

Data characterisation conducted
No